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Title:

Resuscitation using less fluid does not have a negative impact on hydration status in children with moderate sized scalds: a prospective single-centre UK study.

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ABSTRACT

Background

After a burn, optimal fluid resuscitation is critical for positive patient outcome. Although national guidelines advocate using resuscitation fluids of 4 mL per kg body weight and percent Body Surface Area (%BSA) for paediatric burns of >10% BSA, evidence in adults suggest that such volumes lead to over-resuscitation and related complications. Our aim was to investigate whether children managed with biosynthetic dressings (BiobraneTM) and reduced fluid volumes remain well hydrated, as determined by clinical and laboratory parameters.

Methods

At a single UK Burn Centre, children with scalds of 10-19%BSA managed with Biobrane were given 80% maintenance fluids and no formal burn resuscitation (permissive hypovolaemia [PH] group). Urine output (UO), serum sodium, urea, and creatinine were used as 24-hour markers of hydration and concentrations compared to those in a patient cohort treated within the same centre when traditional resuscitation was used (TR group).

Results

Serum sodium concentrations and UO in the PH group were similar to those in the TR group (median sodium: PH = 136, TR = 136, $P=1.00$; median UO: PH = 1.5, TR = 1.8, $P=0.25$). Urea concentrations were lower and creatinine concentrations higher in the TR group compared to the PH group (median urea: PH = 3.2, TR = 2.3, $P=0.04$; median creatinine: PH = 21, TR = 30, $P<0.001$). A higher proportion of TR patients than PH patients fell outside the reference ranges for urea (61% vs. 23%; $P=0.04$) and creatinine (44% vs. 8%; $P=0.03$).

Conclusion

Based on markers of hydration, children with moderate-sized scalds managed with Biobrane can be safely managed with less fluid.

List of abbreviations:

BSA – Body Surface Area

UO – Urine output

PH - Permissive Hypovolaemia

TR – Traditional Resuscitation

IQR – Inter Quartile Range

SWCBC – The South West Children's Burns Centre

IV – Intravenous

Keywords: pediatric burns, fluid resuscitation, hydration, permissive hypovolemia, Parkland Formula

INTRODUCTION

Treating burned patients with appropriate and timely fluid resuscitation early after injury is critical to outcome and survival [1-6]. Under-resuscitation is known to lead to poor clinical outcome due to organ hypo-perfusion [7] and the possibility of burn depth conversion [8, 9]. Over-resuscitation, or fluid overload, has been shown to increase the likelihood of complications such as respiratory compromise, sepsis, multi-organ failure and death, due to fluid accumulation, oedema formation and compartment syndrome [4, 10, 11]. It can also lead to deepening of the burn wound, resulting in longer healing times and potentially scarring [8].

Although national guidelines state that children who have sustained a burn of more than 10% of body surface area (BSA) should receive traditional fluid resuscitation according to the Parkland formula at 4mL/kg/%BSA [12], a growing body of evidence in adult patients shows that such volumes lead to over-resuscitation and high-risk complications [4, 13-16]. Some centres have therefore adopted an alternative method, permissive hypovolaemic resuscitation, using decreased fluid volumes aiming to simply maintain organ perfusion [17]. However, as evidence supporting the effectiveness and safety of such a regimen in paediatric burns patients is currently limited, many places in the UK still opt to follow the traditional Parkland formula [18].

Prior to 2007, The South West Children's Burns Centre (SWCBC) used a resuscitation regimen based on the Parkland Formula, which recommended starting resuscitation at 10% BSA but with an initial reduced rate of 3mL/kg/%BSA and 100% maintenance fluid (hereafter referred to as traditional regimen [TR]). All fluid administered was Hartmann's solution. In January 2007, following a local audit of outcomes including hyponatraemia, the SWCBC changed to a permissive hypovolaemic fluid resuscitation regimen. Children with partial thickness scalds

who had biosynthetic dressings (Biobrane™) applied were resuscitated starting at a BSA of >15% and a rate of 2mL/kg/%BSA with 80% maintenance fluid. Published research from this centre has shown that using the 2mL/kg/%BSA regimen resulted in the use of 41% less fluid than used across other England and Wales services and resulted in improved outcomes; hospital length of stay per %BSA was significantly shortened and fewer patients required skin grafts than those treated before 2007 [18]. In 2011, following good results and with agreement from the local paediatric management team and burns team, the protocol was further adjusted and the burn size at which to start resuscitation was increased from 15% BSA to 19% BSA. Using this new regimen, patients with scalds of 10-19% BSA were not formally resuscitated and given 80% maintenance fluid alone (hereafter referred to as the permissive hypovolaemic [PH] group).

Although emerging evidence from the centre has shown promising result using reduced fluids, we have not formally shown whether children managed with less fluid remain adequately hydrated in the first 24 hours, during which time fluid loss is greatest and the risk of complications highest [19]. The aim of this study was to provide evidence that a permissive hypovolaemic regimen can provide adequate hydration and is safe in children with moderately sized scalds, as demonstrated by laboratory serum and urine markers of fluid status.

METHODS

Patients

All children aged between six months and 15 completed years with a partial thickness scald of between 10-19% BSA managed with Biobrane and admitted to the SWCBC between April 2011 and Dec 2014 were included. Inclusion and exclusion criteria are shown in Table 1.

Ethical and local Research and Innovation permission were gained prior to study start. Funding was provided by the North Bristol NHS Trust Small Grant scheme.

Clinical management

Clinical management followed the South West burns fluid resuscitation protocol as agreed in 2011 (Figure 1). Children were transferred as soon as possible after referral to the SWCBC, and remained 'nil by mouth' and on 80% intravenous maintenance fluids until a formal theatre assessment or assessment under oral sedation had been conducted. If the clinician caring for the child in the referring hospital considered that the child required fluid resuscitation then a bolus of 10mls/kg of 0.9% saline were given and the child reassessed. After arrival at the SWCBC, children were transferred to theatre within 24 hours (median [IQR]: 7 hrs [3.5 – 11]) and Biobrane applied under general anaesthesia according to standard practice. Once the child returned to the ward after being assessed in theatre or under sedation as having an injury of between 10-19% TBSA, the parents, and child if age appropriate, were approached for consent. No family declined study participation.

Sampling

Blood samples to measure baseline levels of serum urea, creatinine and other electrolytes were collected in theatre. Back on the ward, children received routine post-operative follow-up care, involving observation of the child's clinical condition, a record of fluid intake, and urine output (mL/kg/hr). Routine blood tests were taken at 24 hours after injury to assess serum sodium (mmol/L), urea (mmol/L) and creatinine (μ mol/L) concentrations. Blood glucose was also measured as part of normal practice. The only addition to routine monitoring was an additional test for serum osmolality (mOsm/kg). The amount of fluids received in the Emergency Department, during transfer and in theatre was noted as well as any requirement for further

intravenous fluid boluses. If at any point a child showed signs of dehydration (based on clinical parameters), they received treatment as necessary without delay.

Comparison with historical regimen

To compare concentrations of measured biochemical markers in those children managed with less fluid (PH group) to children who received more fluid with the traditional regimen (TR group), we used retrospective data on the same parameters collected on patients managed at the centre in 2005/2006. We compared 24-hour serum sodium, urea and creatinine concentrations and urine output. Although the majority (9/11, 82%) of PH patients had serum osmolality values within the reference range, a comparison with the TR group was not possible as this parameter was not available in the TR group. Apart from the difference in fluid regimens, patients were managed in exactly the same way. Secondary outcomes such as skin grafting rates and length of stay were not compared as these data have been previously published [18].

Statistical analyses

All analyses were performed in Stata v. 14 [20]. Summary statistics used were medians and inter quartile range (IQR). All categorical patient characteristic variables were analysed using Fisher's exact tests. Differences in marker concentrations between PH children and TR children were analysed using Mann-Whitney U tests. Effect sizes were calculated if $P < 0.05$. For Mann-Whitney U tests, effect size was displayed as r where the standard values of r for small, medium, and large sizes are 0.1, 0.3 and 0.5 respectively. We used two-sample proportion tests to compare the proportion of patients outside the reference ranges in both groups. Odds ratios and 95% confidence intervals were used as a measure of effect size for proportion tests.

Differences between the two groups at baseline was only analysed if a difference was found at 24 hours.

Missing data was handled using multiple imputation. Multiple imputation is a common technique used to correct for bias introduced by missing data [21]. We used multiple imputation by chained equations using the “mi” command with 40 imputations. All laboratory parameters were skewed and therefore included in the imputation model using predictive mean matching (N=25 set as the number of closest observations/nearest neighbours from which to draw imputed values). To improve model performance, we also included four auxiliary variables: age, gender, length of stay and burn size. Model diagnostics for imputed data were performed using the command ‘midiagplots’.

RESULTS

Patients

In total, 15 patients managed with the permissive hypovolaemic regimen (PH group) were included in the study. Two patients were excluded in the analyses due to wrong samples being taken. All 13 remaining patients had scalds classified as partial thickness. Data was available for 26 patients managed under the traditional regimen (TR group). There was no difference in age (median [IQR]: PH: 15 months [13-16], TR: 19 months [15-29], $P = 0.11$), gender distribution (PH: 69% males, TR: 67% males, $P = 0.60$) or burn size (median [IQR] BSA: PH: 12% [11-13], TR: 13% [11-14], $P = 0.67$) between the two groups. No child was hypoglycaemic at any point during the study. In total (including fluids received during transfer, in theatre or extra intravenous boluses), patients in the PH group received a median of 200 mL (IQR: 150-312) of intravenous (IV) fluids during treatment. This is less fluid than the predicted median fluid intake based on their weight and %BSA had they been on a 3mL/kg/%BSA

regimen as was the case prior to 2007 (predicted median [IQR]: 420 mL [IQR: 369-537; $P = 0.01$, effect size $r = 0.49$).

Missing data

Between one (8%) and five (39%) PH patients and between eight (31%) and nine (35%) TR patients had data missing for our chosen hydration markers (Table 2). However, we saw very little change in the measured variables using multiple imputation compared to all available data (Appendix table A). We therefore present the results using all available data.

Clinical markers

At 24 hours, serum sodium concentrations and urine output were no different between PH and TR patients and the proportion of individuals outside the reference ranges for these two parameters were similar (Table 2; Figure 2). It is noteworthy however, that the patients with concentrations outside the reference ranges in the PH group were very close to the reference range values whereas patients in the TR group showed more extreme concentrations (Figure 2). Serum urea and creatinine concentrations at 24 hours did differ between the two groups, however, with urea being lower and creatinine higher in the TR group (Table 2). Concentrations in the TR group were very close to the lower (urea) and higher (creatinine) end of the reference range and a higher proportion of individuals were outside the norm for these two parameters (Table 2; Figure 3). These differences between groups were not seen at baseline (Table 2).

DISCUSSION

We found that, based on clinical and laboratory parameters of hydration status, patients managed with Biobrane and a permissive hypovolaemic burn resuscitation regimen remained adequately hydrated at 24 hours. For the majority of patients, serum sodium, urea and creatinine concentrations, and urine output were well within recommended reference ranges and if anything indicated a slightly more normal hydration status than those managed historically using more fluids.

Getting the timing and fluid volumes right after a burn is essential for a positive patient outcome [2]. Although the Parkland formula is easy to use, a growing body of published evidence in adults suggest that this volume of fluid can lead to over-resuscitation and significant complications [17]. In the SWCBC, it is the standard of care to apply Biobrane for children with partial thickness scalds of moderate size as soon as possible after admission. Repeated local audits and published literature [17, 3, 22] have shown that children managed in this way required less fluids in order to improve outcomes. A previous retrospective audit published by Walker et al. [18] looked at the effect on patient outcome in the SWCBC before 2007 when patients were resuscitated using a rate of 3mL/kg/%BSA and after 2007 when resuscitation using a reduced rate of 2mL/kg/%BSA was in place. They showed that length of stay per %BSA was significantly reduced after 2007 with all other care maintained the same. This suggests that patients receiving less fluid may be less likely to develop complications associated with over-resuscitation as such complications would prolong their length of stay. The authors also showed that numbers of skin grafts were fewer and readmission rates comparable to those seen prior to 2007 indicating no compromise of burn depth, a problem seen with under-resuscitation [7-9].

Here, the main aim was to determine whether using no formal fluid resuscitation for children with scalds of <20% BSA managed with Biobrane is safe, as assessed by biochemical and clinical markers of hydration. The widely used laboratory parameter used to determine adequate resuscitation in the literature is urine output and using the traditional regimen is recommended to be between 1 and 2 mL/kg/hr depending on age. Our results show that urine output was comparable in the two groups. Very few PH patients were outside the reference range and although a larger proportion of TR patients were, this difference was not significant. Of note, studies have shown that caution is needed if only looking at urine output as a marker as the surge in vasopressin production post burn [23] can cause misleading results. However, the other markers we used indicated similar results. Serum sodium concentrations were comparable in the two groups and very rarely outside the reference range, hence do not indicate any adverse vasopressin-mediated responses to volume depletion or stress. For urea and creatinine, the PH group showed concentrations closer to the normal range; the traditional group had a higher proportion of individuals outside the reference ranges for both these markers with concentrations very close to the lower and higher end of normal. Although the slightly higher urea in the PH group at 24 hours could reflect a small reduction in renal perfusion in that group, the differences in creatinine at 24 hours simply mirror baseline differences.

Limitations with this study included a small sample size. However, the study did benefit from blood tests at both baseline and 24 hours which allowed each patient to act as its own control. Another limitation was the large proportion of missing data, particularly at baseline, but multiple imputation results were very similar to those using all available data rendering introduced bias due to missing data unlikely. We were not able to standardise burn depth, but all burns were determined to be partial thickness scalds by consultant burn surgeons and there were no issues with dressing adherence which might indicate deeper burns. There were additional parameters not collected in this study that would have been interesting to compare

such as blood lactate levels and body weight. It would be useful to add these to any future research protocol.

CONCLUSION

The majority of burn services in England and Wales use resuscitation volumes based on the Parkland Formula of between 3 and 4mL/kg/%BSA [18]. There is still a considerable variation in fluid resuscitation protocols between services, representing a lack of consensus in how moderate sized partial thickness scalds in children should be resuscitated and very little high quality evidence is available to guide practice [24, 25]. Most of the literature reporting problems with using a large volume of fluid arise from research on adult burns, but evidence is emerging that the same may be true in children. It could be argued that scalds of this size (10-20% BSA) need little if any intravenous resuscitation. One study published by Greenhalgh in 2010 [26] showed that 82% of clinicians of varying experience from all continents except Africa who responded to a survey, stated they were comfortable using only oral hydration for burns <15% BSA. In addition to this study indicating that children with moderate scalds can be safely managed with less fluid than dictated by current guidelines, previous research from our centre has identified [18] that such patients show significantly improved outcomes such as reduced length of stay and skin grafting rates compared to traditionally treated patients. Another study showed that paediatric patients receiving less fluid have similar urine output, resulting in a less positive fluid balance, and lower incidence of renal failure [6].

A large multicentre randomised controlled trial is now needed to adequately evaluate and compare reduced fluid regimens to those currently recommended in national protocols.

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COMPETING INTERESTS

None declared.

REFERENCES

[1] Jeschke MG, Barrow RE, Wolf SE, Herndon DN. Mortality in burned children with acute renal failure. *Arch Surg* 1998;133:752–6.

- [2] Barrow RE, Jeschke MG, Herndon DN. Early fluid resuscitation improves outcomes in severely burned children. *Resuscitation* 2000;45:91–6.
- [3] Hoskins SL, Elgjo GI, Lu J, Ying H, Grady JJ, Herndon DN, Kramer GC. Closed-loop resuscitation of burn shock. *J Burn Care Res* 2006;27:377–85.
- [4] Klein MB, Hayden D, Elson C. The association between fluid administration and outcome following major burn: a multicenter study. *Ann Surg* 2007;245:622–8.
- [5] Santry HP, Alam HB. Fluid resuscitation: Past, present, and the future. *Shock* 2010; 33:229–41.
- [6] Kraft R, Herndon DN, Branski LK, Finnerty CC, Leonard KR, Jeschke MG. Optimized fluid management improves outcome of pediatric burn patients. *J Surg Res* 2013;181:121–8.
- [7] Brusselaers N, Monstrey S, Colpaert K, Decruyenaere J, Blot SI, Hoste EA. Outcome of acute kidney injury in severe burns: a systematic review and meta-analysis. *Intensive Care Med* 2010;36:915–25.
- [8] Singh V, Devgan L, Bhat S, Milner SM. The pathogenesis of burn wound conversion. *Ann Plast Surg* 2007;59:109–15.
- [9] Kim DE, Philips TM, Jeng JC, Rizzo AG, Roth RT, Stanford JL *et al.* Microvascular assessment of burn depth conversion during varying resuscitation conditions. *J Burn Care Rehabil* 2001;22:406–16.
- [10] Gore DC, Hawkins HK, Chinkes DL, Chung DH, Sanford AP, Herndon DN *et al.* Assessment of adverse events in the demise of pediatric burn patients. *J Trauma Injury Infect Crit Care* 2007;63:814–18.
- [11] Saffle JR. The phenomenon of “fluid creep” in acute burn resuscitation. *J Burn Care Res* 2007;28:382–95.

- [12] Baxter CR, Shires T. Physiological response to crystalloid resuscitation of severe burns. *Ann N Y Acad Sci* 1968;150:874–894.
- [13] Engrav LH, Colescott PL, Kemalyan N, Heimbach DM, Gibran NS, Solem LD *et al.* A biopsy of the use of the Baxter formula to resuscitate burns or do we do it like Charlie did it? *J Burn Care Rehabil* 2000;21:91–5.
- [14] Pruitt BA Jr. Protection from excessive resuscitation: pushing the pendulum back. *J Trauma* 2000;49:567–8.
- [15] Cartotto RC, Innes M, Musgrave MA, Gomez M, Cooper AB. How well does the Parkland formula estimate actual fluid resuscitation volumes? *J Burn Care Rehabil* 2002;23:258–65.
- [16] Cancio LC, Chavez S, Alvarado-Ortega M, Barillo DJ, Walker SC, McManus AT *et al.* Predicting increased fluid requirements during the resuscitation of thermally injured patients. *J Trauma* 2004;56:404–13.
- [17] Arlati S, Storti E, Pradella V, Bucci L, Vitolo A, Pulici M. Decreased fluid volume to reduce organ damage: a new approach to burn shock resuscitation? A preliminary study. *Resuscitation* 2000;72:371–8.
- [18] Walker TL, Rodriguez DU, Coy K, Hollén LI, Greenwood R, Young AE. Impact of reduced resuscitation fluid on outcomes of children with 10-20% body surface area scalds. *Burns* 2014;40:1581–6.
- [19] Ahrns KS. Trends in burn resuscitation: shifting the focus from fluids to adequate endpoint monitoring, edema control and adjuvant therapies. *Crit Care Nurs Clin North Am* 2004;16:75–98.
- [20] StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.

- [21] Sterne JA, White IR, Carlin JB, Spratt M, Royston P, Kenward MG *et al.* Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;38:b2393.
- [22] Holm C, Mayr M, Tegeler J, Hörbrand F, Henckel von Donnersmarck G, Mühlbauer W *et al.* A clinical randomized study on the effects of invasive monitoring on burn shock resuscitation. *Burns* 2004;30:798–807.
- [23] Carajal H. Fluid resuscitation of pediatric burn victims: a critical appraisal. *Pract Pediatr Nephrol* 1994;8:357–66.
- [24] Henschke A, Lee R, Delaney A. Burns management in ICU: Quality of evidence. *Burns* 2016;42:1173–82.
- [25] Guilabert P, Usúa G, Martin N, Abarca L, Barret JP, Colomina MJ. Fluid resuscitation management in patients with burns: update. *Brit J Anaesth* 2016;117:284–96.
- [26] Greenhalgh DG. Burn resuscitation: The results of the ISBI/ABA survey. *Burns* 2010; 36:176–182.

Table 1. Inclusion and exclusion criteria for study participants.

	Inclusion criteria	Exclusion criteria
Size	All 10-19% BSA scalds assessed at SWCBC by burn surgery consultant in theatre.	Scalds <10% or >19% BSA.
Type of burn	Partial thickness scalds only.	Flame, chemical and electrical burns, full thickness scalds or burns.

Dressing application	Scalds receiving Biobrane™ within 24 hrs.	Any scald not receiving Biobrane™ within 24 hrs.
Age	All children between 6 months and 15 completed years.	Children younger than 6 months or 16 years or older.

Table 2. Biochemical markers indicating hydration status at 24 hours post admission in patients where a permissive hypovolaemic resuscitation regimen was used (PH group) and in those where a traditional resuscitation regimen was used (TR group). Baseline values displayed for parameters that were different between the two groups.

	Reference range	PH-group				TR-group				P-value [†]	P-value ^{††}
		N	Median (IQR)	Min-Max	Out of range N (%)	N	Median (IQR)	Min-Max	Out of range N (%)		
24 hours											
Serum sodium (mmol/L)	133-146	13	136 (135-138)	129-140	1 (8)	18	136 (134-139)	129-141	2 (11)	1.00	0.78
Serum urea (mmol/L)	2.5-6.5	13	3.2 (2.5-5.0)	1.6-5.4	3 (23)	18	2.3 (1.5-3.0)	0.5-7.3	11 (61)	0.04 <i>r</i> = 0.39	0.04 OR (95% CI) = 0.19 (0.04-0.95)
Serum creatinine (μmol/L)	15-31	13	21 (19-23)	16-37	1 (8)	18	30 (27-38)	21-82	8 (44)	<0.001 <i>r</i> = 0.66	0.03 OR (95% CI) = 0.10 (0.01-0.98)
Urine output (mL/kg/hr)	0.5-2*	12	1.5 (1.1-1.9)	0.5-2.5	2 (17)	18	1.8 (1.0-3.0)	0.7-4.8	8 (44)	0.25	0.12
Baseline											
Serum urea (mmol/L)	2.5-6.5	8	4.0 (3.6, 4.8)	3.0-6.4	0 (0)	17	3.7 (2.9, 5.6)	1.6-11.3	5 (29)	0.73	0.09
Serum creatinine (μmol/L)	15-31	8	23 (22, 25)	18-70	1 (13)	17	29 (24, 39)	14-73	8 (47)	0.08	0.10

* Concentrations down to 0.5 mL/kg/h are allowed as long as patient is well perfused and not acidotic [18].

† P-values stem from Mann-Whitney U-tests comparing the actual concentrations of each measure between the two groups. Effect size (*r*) displayed if $P < 0.05$.

†† P-values comparing the proportions out of reference range in the two groups (2-sample proportion test). Effect size (OR + 95% confidence intervals) displayed if $P < 0.05$.